Remarks/Arguments:

The specification has been amended. The existing title has been replaced with a new title. A cross-reference to the related applications has been added. Moreover, Applicants have deleted the existing sequence listing and placed it with the substitute sequence listing enclosed herewith. Also, paragraphs at page 7, line 19; page 8, line 18 and page 9, line 1 have been amended so as to include references to the Sequence Identifier Numbers for nucleotide sequences depicted in Figures 1A, 1B, 4 and 5. Furthermore, the paragraph at page 28, line 1 has been amended to include the generic terminology for "TAB®".

The claims have also been amended. In particular, claims 1 and 7 have been amended to better define the subject matter of the present invention.

Moreover, new claims 32-56 are presented herewith to more fully define the present invention.

Specification/Informalities

Each of the formalities have been addressed in the amendments presented herewith. Moreover, Applicants have enclosed substitute computer-readable and paper copies of the sequence listing, and a statement regarding the substitute copies of the sequence listing.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 1 (claims 2-4 dependent therefrom) and 5-7, as allegedly being incomplete for omitting essential elements.

Moreover, the Examiner alleges that claim 7 is unclear and states the following:

> **Claim 7 is unclear in the recitation of "a disease associated with a nonsense mutation in a gene modulating the function of a eukaryotic peptidyl transferase." It is unclear from the specification and the claims as to the scope of the diseases that are meant to be encompassed by this term, particularly as it is unclear as to how the disease is "associated" with a nonsense mutation. In the interest of advancing prosecution, the examiner has interpreted viral infection and HIV as being encompassed by the term "a disease associated with a nonsense mutation in a gene modulating the function of a eukaryotic peptidyl transferase." It is suggested that applicants clarify the meaning of the claim.**

Claim 1 has been amended so as to more clearly define the subject matter of the present invention. As recited in claim 1, the result or outcome is one of the therapeutic effect of the drug on the patient. The therapeutic effect is that of modulating programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay, which have defined pharmacological implications. Claims 5-7 relate to methods for treating viral infections or a disease resulting from a nonsense mutation according to the method of amended claim 1.

Claim 7 now recites, in method, a disease resulting from a nonsense mutation. Also, new claims 48-50 are presented herewith to more fully define this subject matter. Clear support for these claims can be found in the application as filed. For example, as described in Applicants' specification (at page 36, lines 12-31 and page 37, lines 1-4), the nonsense-mediated mRNA decay pathway regulates decay of transcripts that have acquired nonsense codons through a mutagenic event. Modulating the nonsense-mediated mRNA decay pathway can overcome lack of gene expression due to a nonsense mutation.

The Examiner has incorrectly interpreted viral infection and HIV as being encompassed by the term "a disease associated with a nonsense mutation in a gene . . . ". It would be known to one of ordinary skill in the art that a nonsense mutation is a single base pair substitution that

prematurely codes for a stop in amino acid translation (stop codon). A gene that carries a nonsense mutation produces an abnormally short protein that causes disruption in the cell. Nonsense mutations are found in many genes that result in diseases, such as those listed in new claim 50. The present invention is directed, in part, to using specific drugs to stabilize nonsense-containing mRNA, which leads to a nonsense suppression phenotype. By stabilizing the nonsense mRNA, the likelihood of "read-through" transcripts is dramatically increased, so as to allow for enough expression of the protein to overcome the pathological phenotype (see page 7, lines 1-8).

Whereas diseases, such as those recited in claim 50, are associated with nonsense mutations, the ability of a virus to propagate in an infected individual is dependent on programmed ribosomal frameshifting. As would be known to one of ordinary skill in the art, ribosomal frameshifting is a directed change in translational reading frames that allows the production of a single protein from two or more overlapping genes. It has been described mainly in viruses, but also in some cellular genes. The present invention is directed, in part, to using specific drugs that either increase or decrease the efficiency of frameshifting. As described on page 5, lines 20-26, changing the efficiency of ribosomal frameshifting alters the ratio of certain proteins expressed by viral genes. The end result is interference in the production of viral products.

In view of the foregoing, it should be clear that viral infection and HIV are <u>not</u> encompassed by the term "a disease associated with a nonsense mutation in a gene . . .".

Since these rejections have been addressed by the amendments and remarks presented herewith, Applicants respectfully request withdrawal of these rejections.

Claim Rejections – 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-3, 5 and 7 under 35 U.S.C. §112, first paragraph. In particular, the Examiner alleges that Applicants' specification discloses only two representative species of drugs that affect the peptidyl transferase center, i.e., the antibiotics sparsomycin and anisomycin.

The Examiner has also rejected claims 1-7 under 35 U.S.C. §112, first paragraph. In particular, the Examiner alleges that claims 1-7 are overly broad and that the disclosure is limited to a method for inhibiting function of an eukaryotic peptidyl transferase center *in vitro* by contacting a eukaryotic peptidyl transferase center or a host cell expressing a eukaryotic peptidyl transferase center with an amount of sparsomycin or anisomycin to inhibit the function of a eukayotic peptidyl transferase center.

First of all, Applicants do not agree that the disclosure is limited to only the antibiotics anisomycin and sparsomycin. As the Examiner is aware, Applicant may be his or her own lexicographer. As described on page 19, lines 18-21, the term "drugs" as used in the present application refers to "a compound, such as an antibiotic or protein, that can affect the peptidyl transferase center". The passage further states that the compounds can suppress nonsense mutations, or can increase or decrease (i.e., modulates) frameshift efficiency, which has antiviral consequences. It is noted that Applicants have not departed from the common definition of the term "drug", which is as follows: a substance used in the diagnosis, treatment or prevention of a disease or as a component of a medicine (*The American Heritage College Dictionary, Third Edition*, Houghton Mifflin, Co., NY).

Moreover, Applicants' specification teaches several examples of "drugs", as defined by Applicants, including, but not limited to antibiotics. For example, the drug can be a polypeptide of a ribosome binding protein, L3 (new claim 38). The present inventors discovered that the expression of this polypeptide in cells increased the efficiency of -1

ribosomal frameshifting (see, for example, page 19, lines 13-17 and pages 69-72 of Applicants' specification). Moreover, the specification discloses that the drug can be a vector including a gene encoding a protein involved in programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay (new claim 39). For example, the vector can include a mutant gene selected from the following: *mof4-1*, *mof2-1*, *mof5-1* and human homologues thereof (new claim 40). Also, the specification discloses that the drug can be an expression vector including a nucleic acid hybridizable *in vivo* with an mRNA encoding a wild-type protein involved in programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay, wherein a mutation of a gene encoding the protein changes the efficiency of ribosomal frameshifting (new claim 42). *In vivo* therapy with these gene therapy drugs is discussed, for example, on pages 37-39.

Furthermore, Applicants do not agree with the Examiner's Statements, which allege that the disclosure of the present application fails to provide support for *in vivo* methods. For example, in addition to testing the effects of antibiotics on the efficiency of ribosomal frameshifting using an *in vitro* system, the effects of these drugs on ribosomal frameshifting efficiencies were also examined *in vivo* (see, for example, pages 59 and 60). The antibiotics were also discovered to stabilize nonsense containing mRNAs, leading to a nonsense suppression phenotype *in vivo*. *In vivo* studies were also performed with other drugs.

Based on Applicants' disclosure, a person of ordinary skill in the art would immediately recognize that Applicants had possession of the claimed invention as it pertains to both *in vitro*, as well as *in vivo* applications. The *in vivo* assays show the drugs operating in a cellular environment reflective of the milieu where such compounds would be required to operate.

Moreover, contrary to the Examiner's assertions, Applicants provide clear support in their disclosure for the composition of the drugs, route(s) of administration, dosages and toxicity, such that one of ordinary skill in the art would be able to practice the claimed invention.

For example, with respect to a suitable antibiotic concentration, Applicants describe suitable ranges at page 16, lines 26-30 of the specification. Furthermore, as evidenced by the figures (see, for example, Figure 8), these ranges of drug concentrations were capable of modulating -1 ribosomal frameshifting and/or suppressing the nonsense phenotype. Moreover, from the standpoint of a skilled clinician, the antibiotic compositions are known, and suitable modes of antibiotic administration would be readily determined by the skilled clinician, depending on the site of the infection/disease site and the known structure of the antibiotic. Well known modes for antibiotic administration include intravenous, intramuscular and topical administrations, as well as injection into a body cavity.

Moreover, suitable gene therapy compositions, modes of administration and dosages are disclosed in Applicants' specification and/or in the cited references (for example, on pages 37 and 38).

Applicants submit that they have provided several examples of drugs that can modulate the function of the eukaryotic peptidyl transferase center by modulating ribosomal frameshifting and/or nonsense-mediated mRNA decay. Furthermore, when analyzed from the standpoint of one of ordinary skill in the art (as required), the specification provides the necessary guidance to enable the skilled artisan to practice the claimed invention.

Applicants also submit that they provide clear support in the disclosure for both *in vitro* and *in vivo* methods, as well as working embodiments as they pertain to *in vitro* and *in vivo* applications.

Furthermore, as the Examiner is aware, Applicants are not required to provide evidence of actual success in treating humans or animals for patentability. The requirements under the law should not be confused with the requirements for obtaining governmental approval to market a drug for human consumption.

In view of the amendments and remarks presented herewith, Applicants respectfully request withdrawal of these claim rejections.

Claim Rejections – 35 U.S.C. §102

The Examiner has rejected claims 1-4 under 35 U.S.C. §102(b) as being anticipated by Carrasco et al. (Methods Enzymology 30:282-289). This rejection is respectfully traversed on the basis that this reference fails to teach, disclose or suggest the subject matter of claim 1 as amended.

The present invention is based, in part, on the inventors' discovery that a subset of *mof* alleles affects both programmed -1 frameshifting and nonsense-mediated mRNA decay. The present inventors have discovered that specific agents affect the efficiency of ribosomal frameshifting, and can also affect the nonsense-mediated mRNA decay pathway.

The present invention, as defined in amended claim 1, requires administering to a patient in need thereof a therapeutically effective amount of a drug which modulates programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay. In particular, as more fully defined in new claims 32-50, the drug modulates the efficiency of ribosomal frameshifting, which has antiviral implications, and/or stabilizes nonsense-containing mRNAs, which leads to suppression of the nonsense phenotype.

Carrasco is devoid of any teaching or suggestion with respect to administering a drug to affect programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay. This is because Carrasco is not concerned with the pharmacological implications of administering drugs to patients to treat viral infections or diseases resulting from nonsense-containing transcripts. Instead, Carrasco is directed to *in vitro* methods and systems to study the individual steps of the elongation phase of protein synthesis and of identifying the specific steps of the elongation phase which are affected by anisomycin and sparsomycin.

In summary, Carrasco fails to teach or suggest administering a drug to a patient to affect programmed ribosomal frameshifting (described mainly in viruses) and/or nonsense-mediated mRNA decay, as recited in Applicants' claims.

The Examiner has also rejected claims 1-5 and 7 under 35 U.S.C. §102(b) as allegedly being anticipated by Japanese Patent JP 63146818A, as evidenced by Dinman et al. (PNAS, USA 94:6606-6611). In particular, the Examiner alleges that JP 63146818 teaches a method for treating viral infections by administering anisomycin, and that Dinman, et al. teaches that anisomycin is a peptidyl transferase inhibitor. The Examiner is of the opinion that "the method of treating viral infection by administering anisomycin as taught by JP 63145818 would inherently have affected a eukaryotic peptidyl transferase center." This rejection is respectfully traversed for the reasons set forth below.

JP 63146818 discloses the use of anisomycin as a anti-viral drug. However, this reference fails to teach or suggest administering to a patient a drug which modulates programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay, as now recited in claim 1.

Applicants have discovered that anisomycin and sparsomycin, as well as other drugs specifically alter the efficiency of -1 ribosomal frameshifting, which is neither taught nor suggested by JP 63146818. Moreover, Applicants have discovered that these drugs stabilize nonsense-containing transcripts, which leads to a nonsense suppression phenotype. This has important implications for the treatment of diseases resulting from nonsense mutations, as recited in amended claim 7, and as more fully defined in new claims 48-50 presented herewith.

As mentioned above, the Examiner has incorrectly interpreted viral infection and HIV as being encompassed the term "a disease associated with a nonsense mutation in a gene." The ability to inhibit viral propagation or to suppress a nonsense phenotype are different activities, which Applicants have surprisingly discovered may be associated with the same drug. In this

regard, it is noted that JP 66146818A is not in any way directed to treating a disease resulting from a nonsense mutation.

The Dinman, et al. reference was published in June of 1997-more than 1 ½ years after the earliest priority date (October 6, 1995) and is based, in part, on the present invention. The Examiner appears to rely upon this reference to determine what the level of knowledge is in the art at the time the application was filed. Dinman, et al. is not an effective prior art reference. Therefore, it cannot be used against the present claims. Although Applicants disagree with the Examiner's characterization of Dinman's "universal fact", no further discussion is necessary in view of the amended claims.

In summary, JP 63146818A, as evidenced by Dinman, et al., does not teach or suggest administering a drug so as to specifically affect ribosomal frameshifting and/or nonsense-mediated mRNA decay, as recited in Applicants' claims.

In view of the amendments and remarks presented herewith, Applicants respectfully request withdrawal of these claim rejections.

Claim Rejections – 35 U.S.C. §102/103

The Examiner has rejected claim 6 under 35 U.S.C. 103(a) as being obvious over JP 63146818A, as evidenced by Dinman, et al. In particular, based on this combination, the Examiner alleges that one of ordinary skill would have recognized that anisomycin would have inhibited HIV viral replication.

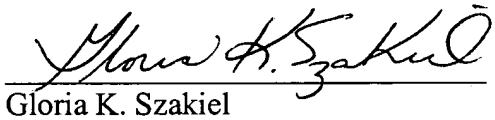
This rejection is respectfully traversed for similarly reasons as those set forth above. In particular, the JP reference, as evidenced by Dinman, et al., does not teach or suggest administering a drug to modulate programmed ribosomal frameshifting and/or nonsense-mediated mRNA decay. As such, withdrawal of the rejection based on these references is respectfully requested.

The Examiner is directed to new independent claim 51 (and new dependent claims 52-56) which include as part of the method for inhibiting the function of the eukaryotic peptidyl transferase center exposing cells to an effective amount of a drug, under conditions and for a sufficient time to change the efficiency of -1 ribosomal frameshifting and/or suppress a nonsense mutation. It is submitted that new claim 51 is patentable over the art.

Applicants submit that the claims, as amended, are patentably distinct over the art and allowable in form. An allowance of the claims is respectfully requested. Should the Examiner have any questions regarding this response, he is encouraged to contact the undersigned.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461.

Respectfully submitted,



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